Remarks

Claims 1, 3-22 and 31 were pending prior to this Response. By the present communication, no new claims have been added, claims 1, 3-17, and 31 have been amended and claims 18-22 have been canceled without prejudice or disclaimer. Support for the amended claims may be found throughout the specification e.g., at page 5, paragraph [0006]; page 6, paragraph [0008]; page 7, paragraph [0010]; and Example 1 on page 25, paragraph [0065] and claims as originally filed. No new matter has been added. Accordingly, upon entry of the present amendment, claims 1, 3-17, and 31 will be pending and under consideration in this application.

Rejections Under 35 U.S.C. §102

Applicants traverse the rejection of claims 1, 3, 10-11, 16-17, and 31 under 35 U.S.C. §102(b) as allegedly being anticipated by Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) in view of Adorjan *et al.* (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9; hereinafter "Adorjan").

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). M.P.E.P. § 2131.

The Office Action alleges (page 3) that Wong discloses a method for producing DNA, wherein a DNA methylation analysis is used comprising genome-wide amplification on genomic DNA and that the amplificates generated are used as a non-methylation standard in the methylation analysis over a linear range citing p. 2619, column 2 and Figure 1A of the reference in support of its position.

As an initial matter, the Office has supplied Adorjan but does not specify the relevance of this reference with respect to the rejection under 35 U.S.C. §102(b). Applicants note that when a rejection relies on inherency, it is incumbent on the Examiner to point to the page and line of the document that justifies the rejection (see for example, *Ex parte Schricker*, 56 USPQ2d 1723 (B.P.A.I. 2000) (unpublished)).

Without acquiescing to the reasoning provided by the Office Action, Applicants have amended independent claim 1 to further define the invention with greater particularity. Claim 1, as amended, recites a method for producing non-methylated DNA for methylation analysis comprising performing genome-wide amplification on genomic DNA using only non-methylated nucleotides or nucleotide triphosphates, thereby producing non-methylated DNA to generate amplificates for use as a non-methylated standard in the methylation analysis over a linear range.

Wong describes the methylation specific analysis of the p16 and p15 promoter region in normal tissues and aneuploid cell populations from patients with Barrett's esophagus. The so-called standard in Figure 1A referred to by the Office Action is a 50-base pair fragment entitled "unmethylated control." It is not clear whether the fragment is wholly non-methylated as a result of using only non-methylated nucleotides, and furthermore only the 50-bp fragment is disclosed. Applicants submit that the document does not disclose a method for the production of genome-wide non-methylated DNA using only non-methylated nucleotides thus, fails to explicitly or inherently teach each and every limitation of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection as it applies to independent claim 1 and claims dependent therefrom is respectfully requested are respectfully requested.

Applicants traverse the rejection of claims 18-22 under 35 U.S.C. § 102(b) as being anticipated by Adorjan *et al.* (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9; hereinafter "Adorjan").

Applicants note that the rejection of claims 18-22 under 35 U.S.C. § 102(b) is rendered moot in view of the cancelation of these claims. Accordingly, withdrawal of the rejection.

Rejections Under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 4-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17, and 31 in view of Apgar *et al.* (Human Immunology, 2003, 64(10), Suppl. 1, p. S86, Abstract).

The U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The new Guidelines establishing standards for obviousness emphasize that Examiners "must provide a reasoned explanation as to why the invention as claimed would have been obvious," and are equally clear that "familiar lines of argument," *e.g.*, a showing of unexpected results, a lack of reasonable expectation of success, and a teaching away from the claimed invention by the prior art, can still demonstrate the non-obviousness of a claimed invention. Applicants submit that the Examiner has not met this burden for the reasons discussed below.

For the reasons discussed above, which are reiterated herein, Applicants submit Wong fails to teach each and every limitation of claims 1, 3, 10-11, 16-17, and 31. Nowhere does Wong expressly or inherently disclose a method for the production of non-methylated DNA as a standard in methylation analysis by performing genome-wide amplification on genomic DNA employing non-methylated nucleotides.

The Office Action has invoked Apgar to remedy the deficiency of Wong with respect to claims 4-7, which directly or indirectly depend from claim 1. Apgar, however, so generally discloses the technology of whole genome amplification that it does not arm the skilled artisan with the necessary tools to perform the modifications to Wong required in order to arrive at the claimed invention. This reference is altogether silent on the subject of DNA methylation and as such neither provides motivation nor suggestion to the skilled artisan to modify the disclosure of Wong in such a way as to arrive at the method of claims 4-7.

The Office Action has rejected claims 6-7 stating (pages 7) that Apgar describes at line 10 of the document using a commercially available kit and alleges that specific

embodiments of the kit (on page 8 of the Office Action) are "GenomiPhi" or "Repli-g". The Office Action further alleges on page 8 that (no citation) "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success."

Schatz et al (Nucleic Acids Research, 2004, Vol. 32, No. 21, e167, p.1-7; hereinafter "Schatz") discloses analysis of CpG methylation patterns using mass spectrometry but makes no mention of performing genome-wide amplification on genomic DNA using only non-methylated nucleotides for the production of non-methylated DNA as a standard for methylation analysis.

The references (Wong, Apgar, and Schatz) cited by the Office Action, either alone or taken together, fail to suggest the desirability of the combination in order to arrive at the method of the present claims with any reasonable expectation of success. The references, alone or in combination, fail to teach or suggest each and every limitation of the present claims, therefore, a showing of prima facie obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

Applicants traverse the rejection of claim 12 under 35 U.S.C. §103(a) as allegedly being unpatentable over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17, and 31 in view of Adorjan *et al.* (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9; hereinafter "Adorjan").

The Office Action states (page 8) that "Wong teaches all of the limitations of claims 1, 3, 10-11, 16-17, and 31" but acknowledges that Wong does not disclose the use of microarray. The Office provides Adorjan in support of its position stating that the reference describes "microarray based DNA methylation analysis."

Claim 12 depends from claim 1 and further limits the methylation analysis by specifying that the genomic DNA is converted into a form, wherein methylated and non-methylated cytosines can be distinguished from one another by means of hybridization, by an amplification and hybridization of the amplificates at oligomer microarrays.

As discussed above, Wong fails to teach each and every limitation of claims 1, 3, 10-11, 16-17, and 31 as Wong does not expressly or inherently disclose a method for the

production of non-methylated DNA as a standard in methylation analysis by performing genome-wide amplification on genomic DNA employing non-methylated nucleotides.

Adorjan, which discloses a micro-array based technique for genome-wide assessment of selected CpG dinucleotides, is similarly silent with respect to genome-wide amplification of non-methylated DNA. Thus, neither Wong nor Adorjan, either alone or in combination, teach or suggest each and every limitation of method as recited in claim 12. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Applicants respectfully traverse the rejection of claim 13 under 35 U.S.C. §103(a) as allegedly being unpatentable over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17, and 31 in view of Tost *et al.* (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10).

The Office Action alleges (on pages 9-10) that Tost describes "an embodiment of claim 1 further comprising performing methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by means of a multiplex PCR."

Claim 13 depends from claim 1 and further limits the methylation analysis by specifying that the genomic DNA is converted into a form, wherein methylated and non-methylated cytosines can be distinguished from one another by means of hybridization by means of a multiplex PCR.

Wong fails to teach each and every limitation of claims 1, 3, 10-11, 16-17, and 31 as Wong does not expressly or inherently disclose a method for the production of non-methylated DNA as a standard in methylation analysis by performing genome-wide amplification on genomic DNA employing non-methylated nucleotides. Tost describes the analysis and quantification of CpG methylation by MALDI mass spectrometry. This document so generally discloses the technology of methylation state analysis that it fails to provide even a departure point to the skilled artisan much less arm them with the tools necessary to implement the technology based on Wong, either alone or in combination, in order to arrive at the present claims. Based on the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Applicants respectfully traverse the rejection of claims 14-15 under 35 U.S.C. §103(a) as allegedly being unpatentable over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17, and 31 in view of Guilleret *et al.* (Int. J. Cancer, 2002, 101: 335-341; hereinafter "Guilleret").

The Office Action alleges (pages 10-11) that Guilleret discloses "an embodiment of claim 1" wherein a mixture of methylated and non-methylated DNA is used as a standard and wherein several mixtures of methylated and non-methylated DNA are used as a standard.

Claims 14-15 depend from claim 1, which is drawn to a method for producing non-methylated DNA for use in methylation analysis by performing a genome-wide amplification on genomic DNA using only non-methylated nucleotides or nucleotide triphosphates to produce fully non-methylated DNA to use as a non-methylated standard in the methylation analysis over a linear range. Claims 14-15 further limit the method of claim 1, by reciting one or more mixtures of known amounts of methylated DNA with known amounts of non-methylated DNA and use of the same as standards.

As discussed above, Wong does not teach each every limitation of the method as claimed. Guilleret discloses the methylation analysis of several CpG cites within the hTERT promoter core region by methylation-sensitive single-strand conformation analysis, however, the reference is silent with regard to genome-wide amplification using only non-methylated nucleotides to produce fully non-methylated DNA for use as a standard in methylation analysis. Guilleret neither provides incentive nor suggestion, either alone or in combination with Wong, to the skilled artisan to modify the disclosure of Wong in such a way as to arrive at the method of claims 14-15. That one of ordinary skill in the art is capable of modifying or combining the disclosures of references does not make the combination prima facie obvious. The mere fact that the disclosures of the documents can be modified or combined is not sufficient to establish motivation or suggestion to combine and make the resultant combination prima facie obvious. Therefore, Applicants submit a prima facie showing of obviousness has not been made. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

The Commissioner is hereby authorized to charge the total amount of $650.00 to cover the payment of a Two-Month Extension of Time fee ($245.00) and a Request for Continued Examination fee ($405.00), small entity. Additionally, the Commissioner is authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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